OFFICE OF NAVAL RESEARCH

CONTRACT N00014-88-C-0118

TECHNICAL REPORT 91-09

THE EFFECTS OF THE INFUSION OF STROMA-FREE HEMOGLOBIN INTO DOGS WITH SPLEENS

BY

C.R. VALERI, L.E. PIVACEK, G. CASSIDY, AND A. GRAY

NAVAL BLOOD RESEARCH LABORATORY
BOSTON UNIVERSITY SCHOOL OF MEDICINE
615 ALBANY STREET
BOSTON, MA 02118

3 JUNE 1991

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER NBRL, BUSM 91-09	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE *(and Subtitle)* THE EFFECTS OF THE INFUSION OF STROMA-FREE HEMOGLOBIN INTO DOGS WITH SPLEENS		5. TYPE OF REPORT & PERIOD COVERED Technical Report 6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) C. Robert Valeri, Linda E. Pivacek, George Cassidy, and Alan Gray		8. CONTRACT OR GRANT NUMBER(s) N00014-88-C-0118
9. PERFORMING ORGANIZATION NAME AND ADDRESS Naval Blood Research Laboratory Boston University School of Medicine 615 Albany St., Boston, MA 02118		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS Naval Medical Research and Development Command Bethesda, MD 20814		12. REPORT DATE 3 June 1991 13. NUMBER OF PAGES 52
14. MONITORING AGENCY NAME & ADDRESS*(if different from Controlling Office)* Bureau of Medicine and Surgery Department of the Navy Washington, D.C. 20372		15. SECURITY CLASS. *(of this report)* Unclassified 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT *(of this Report)*

Approved for public release and sale. Distribution unlimited.

17. DISTRIBUTION STATEMENT *(of the abstract entered in Block 20, if different from Report)*

18. SUPPLEMENTARY NOTES

19. KEY WORDS *(Continue on reverse side if necessary and identify by block number)*

Stroma-free hemoglobin
Oxygen transport capacity
Disseminated intravascular coagulation
Resuscitation fluids
Vasoconstrictor activity
Hemoglobinuria
Renal toxicity

20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

Stroma-free hemoglobin (SFH) solutions may be useful as a resuscitative fluid having oxygen-transporting capacity. SFH modified by intramolecular and intermolecular crosslinking has been shown to have longer vascular retention times. Potential problems with the infusion of SFH include vasoconstrictor effects, renal toxicity, increased methemoglobin levels, and disseminated intravascular coagulation.

In the study reported here, the intravascular retention of crosslinked (bis 3,5-dibromosalicyl fumarate) human hemoglobin (DBBF) and unmodified

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE
S/N 0102-LF-014-6601

UNCLASSIFIED
SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*

bovine hemoglobin (BSFH) and BSFH modified by glutaraldehyde crosslinking were measured in dogs with spleens. The effects on hemodynamics, hematological parameters, coagulation system, and renal function were assessed.

The initial hemoglobin levels following infusion ranged from 900-2700 mg/dl with an intravascular recovery of 30-61%. The circulation of DBBF was longer than either modified or unmodified BSFH. Thirty-eight percent of infused DBBF remained circulating at 24 hours, whereas only 16 to 24% of the BSFH solutions circulated at 6 hours. Hemoglobinuria was not detectable after DBBF infusion. However, hemoglobinuria was present within 30 minutes after infusion of both unmodified and modified BSFH, indicating that the crosslinking of BSFH did not diminish urinary excretion.

All three solutions were associated with increases in total peripheral resistance and mean arterial pressure following infusion, indicating the presence of vasoconstrictor activity. There were no indications of renal toxicity or disseminated intravascular coagulation associated with any of the three hemoglobin solutions.

THE EFFECTS OF THE INFUSION OF STROMA-FREE HEMOGLOBIN INTO DOGS WITH SPLEENS

Valeri CR, Pivacek LE, Cassidy G, Gray A

ABSTRACT

Stroma-free hemoglobin (SFH) solutions may be useful as a resuscitative fluid having oxygen-transporting capacity. SFH modified by intramolecular and intermolecular crosslinking has been shown to have longer vascular rentention times. Potential problems with the infusion of SFH include vasoconstrictor effects, renal toxicity, increased methemoglobin levels, and disseminated intravascular coagulation.

In the study reported here, the intravascular retention of crosslinked (bis 3,5-dibromosalicyl fumarate) human hemoglobin (DBBF) and unmodified bovine hemoglobin (BSFH) and BSFH modified by glutaraldehyde crosslinking were measured in dogs with spleens. The effects on hemodynamics, hematological parameters, coagulation system, and renal function were assessed.

The initial hemoglobin levels following infusion ranged from 900-2700 mg/dl with an intravascular recovery of 30-61%. The circulation of DBBF was longer than either modified or unmodified BSFH. Thirty-eight percent of infused DBBF remained circulating at 24 hours, whereas only 16 to 24% of the BSFH solutions circulated at 6 hours. Hemoglobinuria was not detectable after DBBF infusion. However, hemoglobinuria was present within 30 minutes after infusion of both unmodified and modified BSFH, indicating

that the crosslinking of BSFH did not diminish urinary excretion.

All three solutions were associated with increases in total peripheral resistance and mean arterial pressure following infusion, indicating the presence of vasoconstrictor activity. There were no indications of renal toxicity or disseminated intravascular coagulation associated with any of the three hemoglobin solutions.

INTRODUCTION

Stroma-free hemoglobin (SFH) solutions have oncotic properties and the capacity to transport oxygen and have a potential use as a resuscitation fluid. Concerns in the use of a SFH solution as a blood substitute include vasoconstrictor effects[1-6], kidney toxicity, sterility and endotoxin content, methemoglobin levels, and the potential to precipitate disseminated intravascular coagulation.

When a large amount of free hemoglobin is present in plasma, the haptoglobin binding capacity is saturated, and the excess free tetrameric hemoglobin molecules dissociate into dimers and monomers, which are excreted through renal glomerular filtration into the urine[7-8]. In order to reduce renal excretion and improve intravascular retention, intramolecular and intermolecular crosslinking of stroma free hemoglobin using chemical modification has been developed to decrease the dissociation of the tetramers[8-9].

We have assessed the effects of the infusion of crosslinked (3,4 bis dibromosalicyl fumarate) human stroma-free hemoglobin and unmodified bovine stroma-free hemoglobin and crosslinked (glutaraldehyde) bovine stroma-free hemglobin on hemodynamics, hematological parameters, the coagulation system, and renal function. The intravascular retentions of the stroma-free hemoglobin solutions were measured in dogs with spleens.

OBJECTIVE

Assessment of the effects of infusion of human diasprinated (3,5 bis dibromosalicyl fumarate) stroma-free hemoglobin (DBBF) and modified and unmodified bovine stroma-free hemoglobin (BSFH) on hemodynamics, hematological parameters, coagulation system and renal function.

The clearances of DBBF produced by Baxter Laboratories, Deerfield, IL. and unmodified BSFH, Oxypure, and modified BSFH, Hemopure, produced by Biopure Company, Boston, MA., were measured in dogs with spleens.

METHODS

Six nonsplenectomized dogs weighing between 20 and 24 kilograms were studied. Two dogs were infused with a solution containing 39g of human DBBF stroma free hemoglobin (SFH), two dogs received 40g unmodified BSFH, and two received 42g of modified BSFH.

Experimental Design

On the morning of the study the dogs were sedated with approximately 3.8 mg/kg of acepromazine given orally or with 2.8mg/kg given im. General anaesthesia was maintained with sodium pentathol throughout the study, and muscle relaxation was ensured with pancuronium. Catheterization of a femoral artery with a 20 gauge catheter was performed to permit direct measurement of mean arterial pressure and sampling of arterial blood. Catheterization of a femoral vein with a 16 gauge catheter was also performed to permit withdrawals of blood samples and administration of fluids and drugs. All dogs were intubated 1 hr prior to each experiment and were mechanically ventilated on room air throughout the study.

Measurements were made of the mean arterial pressure (MAP), central venous pressure (CVP), mean pulmonary arterial pressure (MPAP), cardiac output (CO), and heart rate, and blood samples were obtained before infusion of SFH, and at 10, 20, and 40 minutes and 1,2,4 and 6 hours following the infusion for measurement of arterial and

venous oxygen content, arterial ph, arterial blood gases, hemoglobin, hematocrit, white blood cell count, platelet count, creatinine, urea nitrogen (BUN), plasma hemoglobin, plasma methemoglobin, fibrinogen, factor VIII, and fibrin degradation products . In addition, some blood sample measurements were performed at 24, 48, 72 hours and 8 days following transfusion. Urine volumes were recorded, and urea and creatinine levels were measured and clearances calculated.

Cardiac ouput was measured by the thermal dilution method[10] using a cardiac output computer (Instrumentation Laboratories, Lexington, MA). The mean of triplicate measurements of body weight was used to calculate the cardiac index (CI). Total peripheral resistance was calculated from the difference in pressure divided by the flow.

Blood gas and pH measurements were made with standard electrodes and were corrected for body temperature.[10] Hemoglobin and percent saturation were measured by spectrophotometry (IL2, CO-Oximeter). Oxygen content was calculated from the oxygen tension and saturation. Oxygen consumption (V_{O2}) was calculated from the arterial and mixed venous oxygen content and the CI using the Fick equation, and CO2 production was calculated from arterial and venous CO2 content and the CI. The Berggren formula was used to calculate the physiologic shunt Q_s/Q_t during 50% oxygen

breathing. The physiologic dead space fraction V_D/V_t was calculated from arterial and mixed expired CO2 tensions.

The hemoglobin levels in the post infusion plasma samples were measured by the cyanmethemoglobin method modified by decreasing the sample dilution (Boehringer Mannheim Diagnostics, Houston, TX). When plasma hemoglobin concentrations were below 500 mg/dl, the measurements were repeated using a dual beam spectrophotometric method[9]. Methemoglobin measurements were made using the Co-Oximeter (Instrumentation Laboratories, Lexington, MA, Model 282).

Factor VIII and fibrinogen levels were determined using the Coag-A-Mate automated clotting instrument (Organon Teknika, Morris Plains, NJ). Fibrin degradation products were estimated using a Staph Clumping Test (Sigma Chemical, St Louis, MI).

The clearance of the SFH was calculated from the total infused hemoglobin, the measured plasma hemoglobin values following transfusion, and the plasma volume of the recipient dog estimated from weight and previous 51CR blood volume measurements. Changes in the dog's plasma volume due to fluid infused during the study were estimated from changes in the hematocrit values.

RESULTS

The mean 1 hour intravascular recovery of human DBBF SFH was 51% of the total infused and the halftime of this component was approximately 30 hours. The intrasvascular retention of the total infused DBBF SFH at 24 hours measured in one dog was 38% (Figure 1, Table 1a.). There was no detectable hemoglobin excreted in the urine during the 24 hours following the infusion of the DBBF SFH (Table 1d).

There was 30% methhemoglobin present in the plasma during the first 30 minutes following the infusion of the DBBF SFH, which reflected the 25% present in the infused SFH (Figure 4, Table 1a).

The initial 1 hour intravascular recovery of unmodified BSFH was 39-62% of the total infused and the halftime of this component was 4 to 6 hours. The intravascular clearance of modified BSFH was similar to the unmodified BSFH, with a 1 hour recovery of 29-56%, and a halftime of 4 to 6 hours for this component (Figures 2, and 3, Tables 2a and 3a). The intravascular retention of unmodified and modified BSFH over the ensuing 24 hours was much lower than that of the DBBF.

The circulating methhemoglobin was 2-3% following the infusion of unmodified BSFH, and 2-4% following modified BSFH (Figures 5 and 6, Tables 2a and 3a).

In contrast to the DBBF experiments, excretion of the SFH began within 30 minutes after the infusion of either

unmodified or modified BSFH (Tables 2d and 3d). Hemoglobin was present in the urine 24 hours after the infusion of modified BSFH, but none was detectable 24 hours after the infusion of unmodified BSFH.

Serum BUN and creatinine levels decreased immediately following the infusion of DBBF SFH and unmodified and modified BSFH, reflecting hemodilution in the dogs as shown by the hematocrit values (Figures 7 - 15, Tables 1b,2b and 3b). The serum BUN and creatinine levels increased again at 24 hours and 48 hours after infusion. The increases in BUN ranged from 25 to 50% higher than the pre-transfusion levels. The increased levels were explained by separate in-vitro experiments which showed that a 1000-2000 mg/dl concentration of serum hemoglobin increased the measured BUN level by up to 41%.

Reduced concentrations of both BUN and creatinine were noted in the urine during the first 6 hours following the infusions of DBBF SFH and BSFH (Tables 1d, 2d and 3d). Renal function measured using BUN and creatinine clearance were variable, with no apparent correlation to the transfusions.

The arterial-venous differences in oxygen content, oxygen extraction ratios, and oxygen consumption were well maintained following infusion of DBBF SFH and unmodified and modified BSFH. Hemodynamically, all the dogs except one responded to SFH infusion with increases in total peripheral resistance and mean arterial pressure, and reductions in cardiac index and heart rate (Tables 1e, 1f, 1g, 2e, 2f, 2g,

3e, 3f and 3g). The exception was a dog infused with unmodified SFH, and in this dog, the mean arterial pressure dropped by 60% to 81 mmHg at 6 hours following infusion.

Decreases in plasma fibrinogen levels and factor VIII activity were observed after each of the SFH infusions, with subseguent increases to levels exceeding those at baseline. Fibrin degradation products increased slightly at 24 hours (Tables 1c, 2c and 3c).

DISCUSSION

The initial plasma hemoglobin levels in dogs infused with human DBBF SFH solution and unmodified and modified BSFH solutions ranged from 900-2700 mg/dl.

The initial intravascular recovery of the three stroma-free hemoglobin solutions during the first hour following infusion were similar and range from 30-61%. During the subsequent 6 hours, the circulating levels of the DBBF SFH remained stable at approximately 50%, but the unmodified and modified BSFH were cleared faster with 16 to 24% circulating at 6 hours. Twenty-four hours following infusion, 38% of the DBBF SFH remained circulating, and during the 24 to 72 hour period following infusion, more of the DBBF SFH remained circulating than either the unmodified or modified BSFH.

There was no detectable hemoglobinurina following the infusion of DBBF crosslinked SFH, however, crosslinking of the modified BSFH did not prevent rapid urinary excretion. Hemoglobinuria was present within 30 minutes following infusion of both the unmodified and modified BSFH.

The 25% methemoglobin present in the infused DBBF SFH was reflected in a high post infusion methemoglobin level which was cleared along with the oxyhemoglobin.

The increased total peripheral resistance and mean arterial pressure that occured following the infusion of the DBBF SFH and BSFH indicated the presence of vasoconstrictor activity as described by other investigators[1-6]. The

infusion of the hemoglobin solutions did not produce any renal toxicity that could be detected from the BUN and creatinine levels in plasma and urine, and assays of the coagulation system determined that disseminated intravascular coagulation was not present.

The experiments in the dog have provided information concerning the relative retention and excretion of modified and unmodified hemoglobin solutions, their vasoconstrictor properties, and their effects on the coagulation system and the kidneys.

REFERENCES

1. Moss GB, DeWoskin R, Rosen AL, Levine H, Palani CK: Transport of oxygen and carbon dioxide by hemoglobin-saline in the red cell-free primate. Surg Gynec Obstet 142:357-362, 1976.

2. Suaudeau J, Fallon JT, Austen WG, Erdmann AJ: Stroma-free hemoglobin solution for perfusion of the isolated lamb heart at 38C. Trans Am Soc Artif Intern Organs 24:261-268, 1978.

3. Hauser CJ, Kaufman C, Franz R, Shippy C, Schwartz S, Shoemaker WC: Use of crystalline hemoglobin as replacement of RBC mass. Arch Surg 117:782-786, 1982.

4. Moores WY, DeVenuto F, Heydorn WH, Greenburg AG, Utley JR: Effectiveness of stroma-free hemoglobin solution as seen in a right heart bypass swine model. Crit Care Med 10:279-282, 1982.

5. Lieberthal W, Wolf EF, Merrill EW, Levinsky NG, Valeri CR: Hemodynamic effects of different preparations of stroma-free hemolysates in the isolated perfused rat kidney. Life Sci 41:2525-2533, 1987.

6. Vogel WM, Lieberthal W, Apstein CS, Levinsky N, Valeri CR: Effects of stroma-free hemoglobin solutions on isolated

perfused rabbit hearts and isolated perfused rat kidneys. Biomat Art Cell Org 16:227, 1988.

7. DeVenuto F, Friedman HI, Neville JR, Peck CC: Appraisal of hemoglobin solution as a blood substitute. Surg Gynec Obstet 149:417, 1979.

8. Greenburg AG, Peskin GW, Hoyt DB, Moores WY: Is it necessary to improve the intravascular retention of hemoglobin solutions? Crit Care Med 10:266, 1982.

9. Feola M, Simoni J, Canizaro PC, Tran R, Raschbaum G, Behal FJ: Toxicity of polymerized hemoglobin solutions. Surg Gynec Obstet 166:211, 1988.

10. Weisel RD, Vito L, Dennis RC, Valeri CR, Hechtman HB: Myocardial depression during sepsis. Am J Surg 133:512-521, 1977.

11. Blakney GB, Dinwoodie AJ: A spectrophotometric scanning technique for the rapid determination of plasma hemoglobin. Clin Biochem 8:96-102, 1975.

FIGURE 1

The intravascular retention of human DBBF stroma-free hemoglobin.

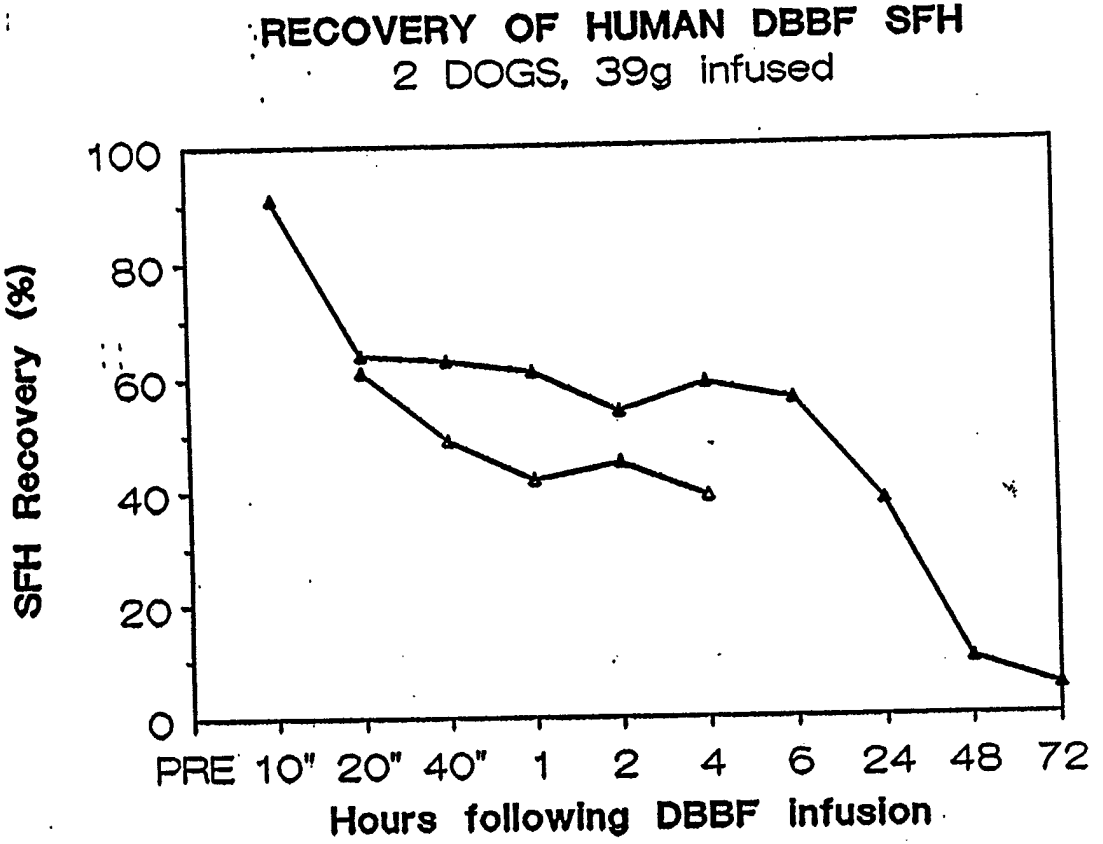
RECOVERY OF HUMAN DBBF SFH
2 DOGS, 39g infused
SFH Recovery (%)
100
80
60
40
20
0
PRE 10" 20" 40" 1 2 4 6 24 48 72
Hours following DBBF infusion

FIGURE 1

FIGURE 2

The intravascular retention of unmodified bovine stroma-free hemoglobin.

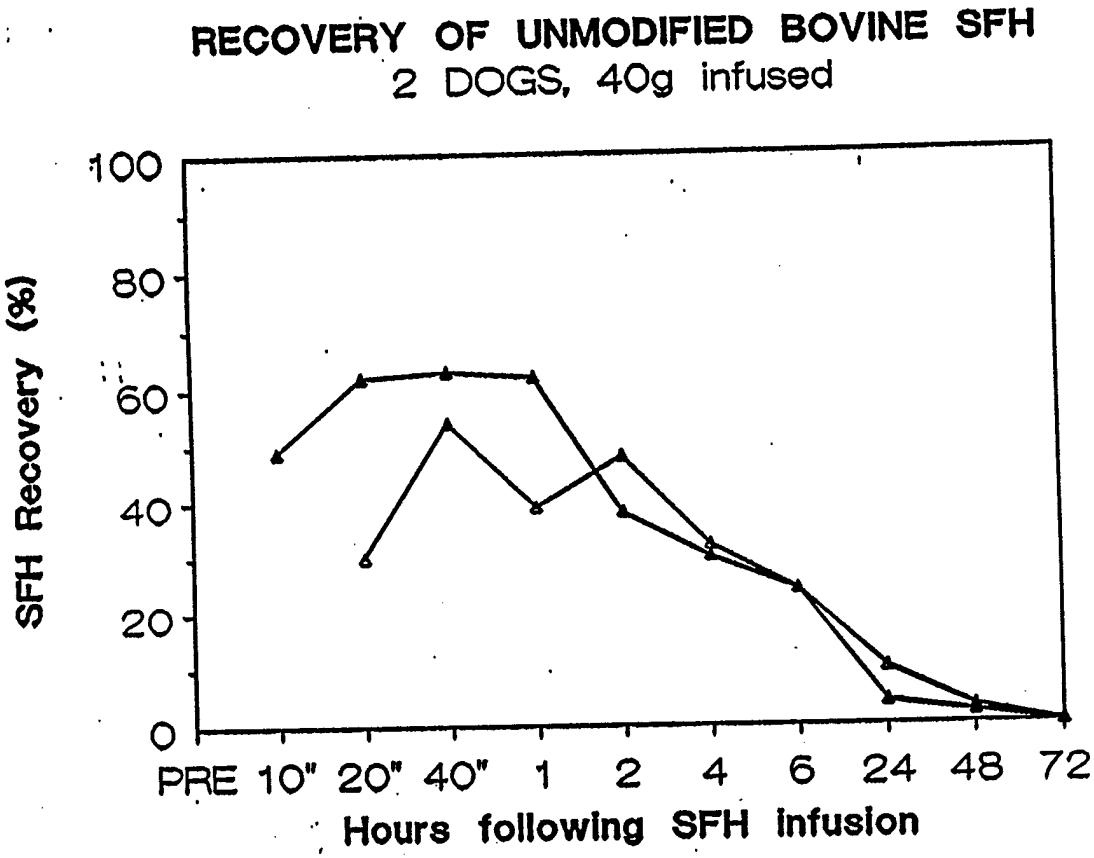
RECOVERY OF UNMODIFIED BOVINE SFH
2 DOGS, 40g infused
SFH Recovery (%)
100
80
60
40
20
0
PRE 10" 20" 40" 1 2 4 6 24 48 72
Hours following SFH infusion

FIGURE 2

FIGURE 3

The intravascular retention of modified bovine stroma-free hemoglobin.

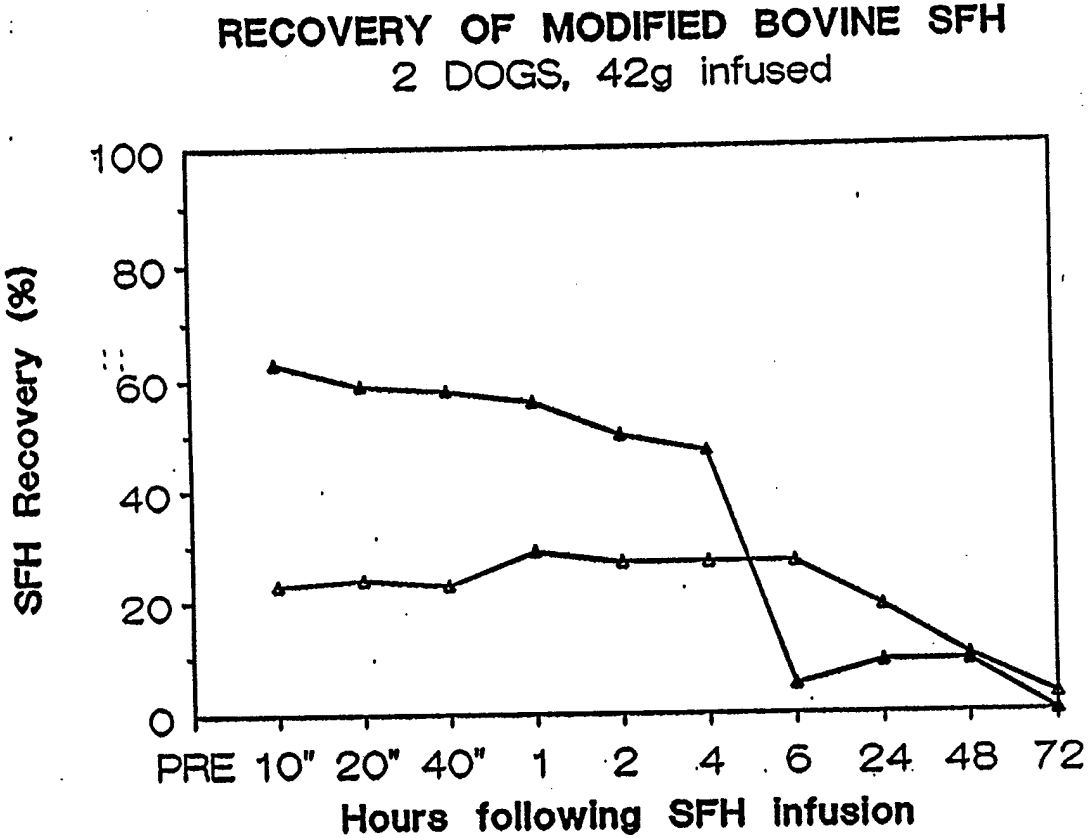
RECOVERY OF MODIFIED BOVINE SFH
2 DOGS, 42g infused
SFH Recovery (%)
100
80
60
40
20
0
PRE 10" 20" 40" 1 2 4 6 24 48 72
Hours following SFH infusion

FIGURE 3

FIGURE 4

Intravascular methemoglobin levels following infusion of human DBBF stroma-free hemoglobin.

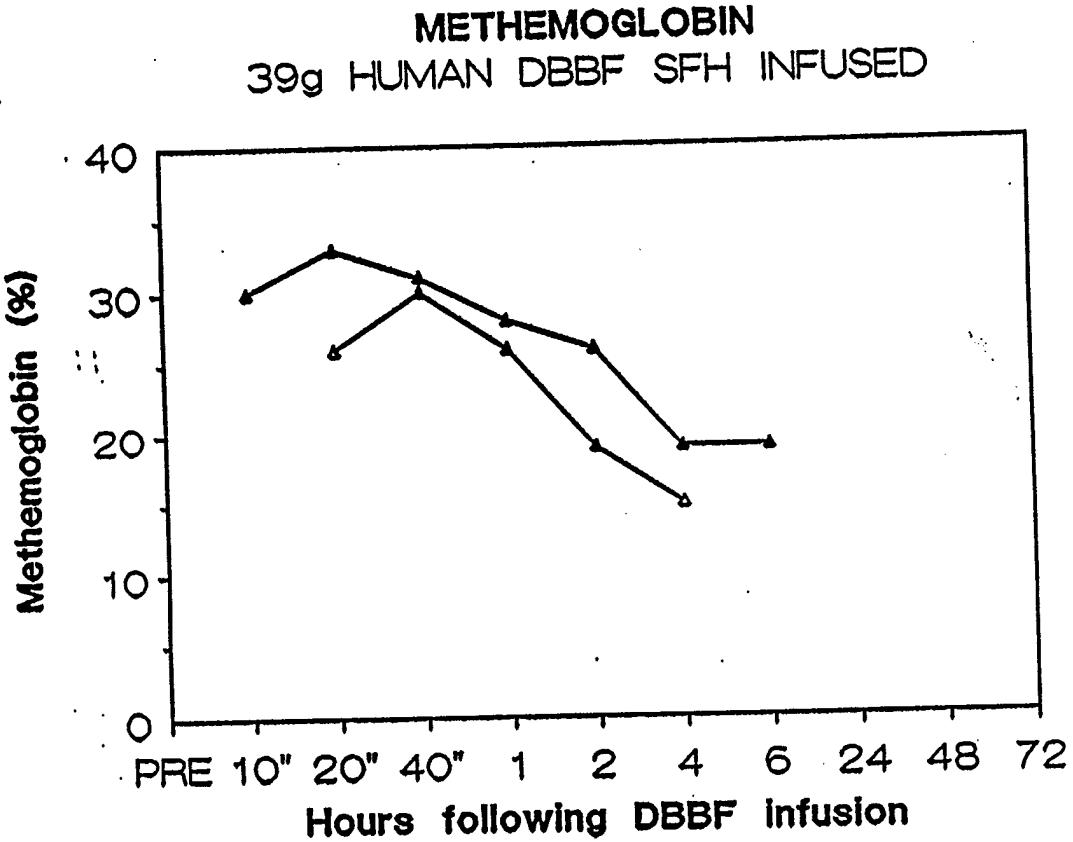
METHEMOGLOBIN
39g HUMAN DBBF SFH INFUSED
Methemoglobin (%)
40
30
20
10
0
PRE 10" 20" 40" 1 2 4 6 24 48 72
Hours following DBBF infusion

FIGURE 4

FIGURE 5

Intravascular methemoglobin level following infusion of unmodified bovine stroma-free hemoglobin.

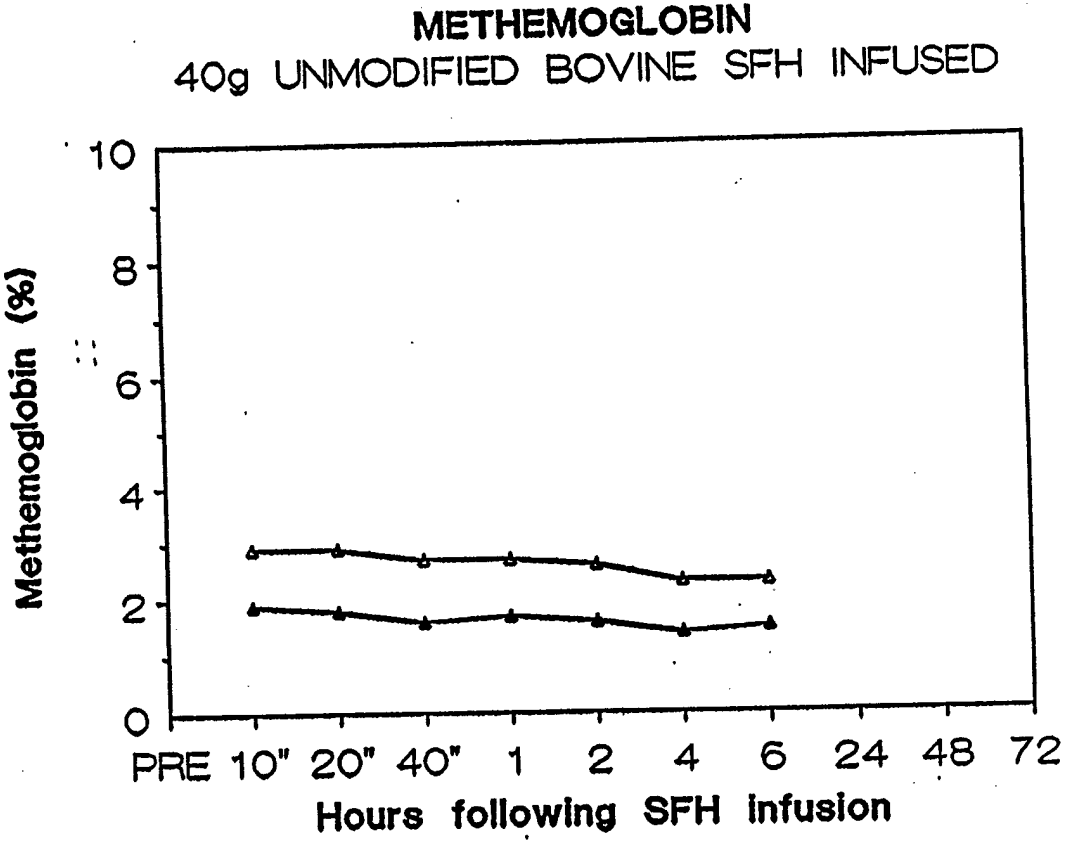
METHEMOGLOBIN
40g UNMODIFIED BOVINE SFH INFUSED
Methemoglobin (%)
10
8
6
4
2
0
PRE 10" 20" 40" 1 2 4 6 24 48 72
Hours following SFH infusion

FIGURE 5

FIGURE 6

Intravascular methemoglobin levels following infusion of modified bovine stroma-free hemoglobin.

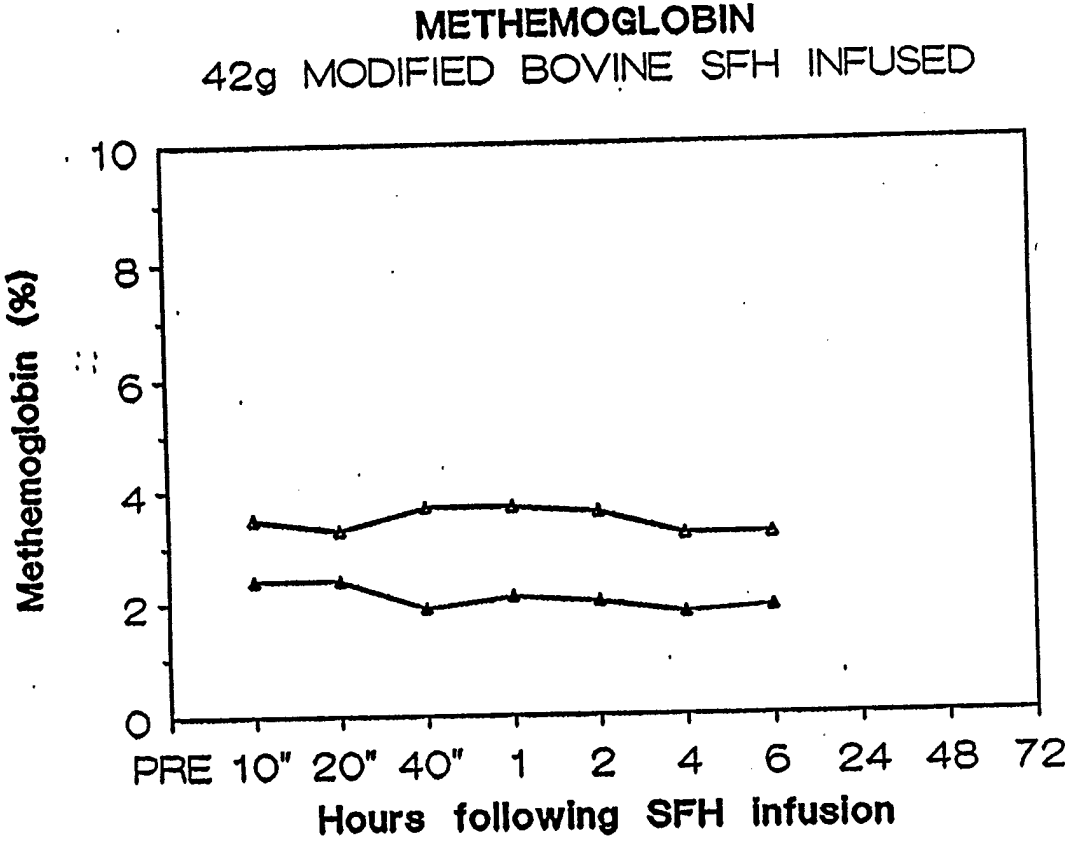
METHEMOGLOBIN
42g MODIFIED BOVINE SFH INFUSED
Methemoglobin (%)
10
8
6
4
2
0
PRE 10" 20" 40" 1 2 4 6 24 48 72
Hours following SFH infusion

FIGURE 6

FIGURE 7

Peripheral venous hematocrit following infusion of human DBBF stroma-free hemoglobin.

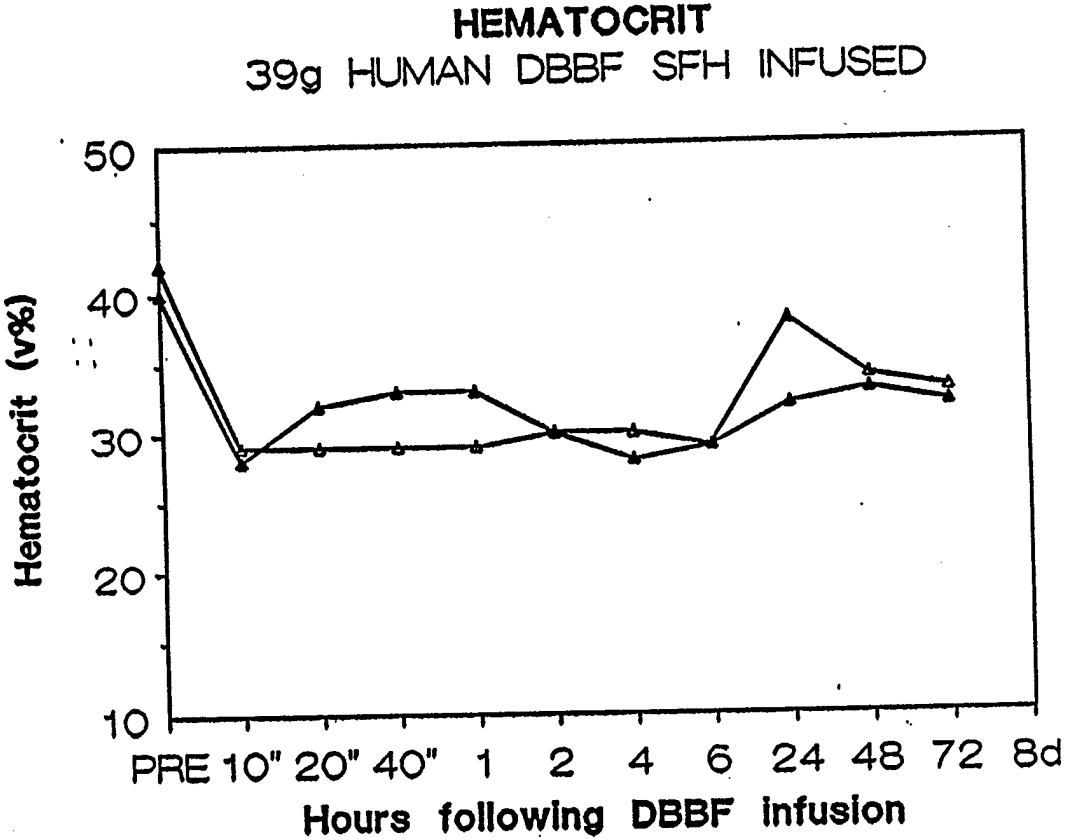
HEMATOCRIT
39g HUMAN DBBF SFH INFUSED
Hematocrit (v%)
50
40
30
20
10
PRE 10" 20" 40" 1 2 4 6 24 48 72 8d
Hours following DBBF infusion

FIGURE 7

FIGURE 8

Peripheral venous hematocrit following infusion of unmodified bovine stroma-free hemoglobin.

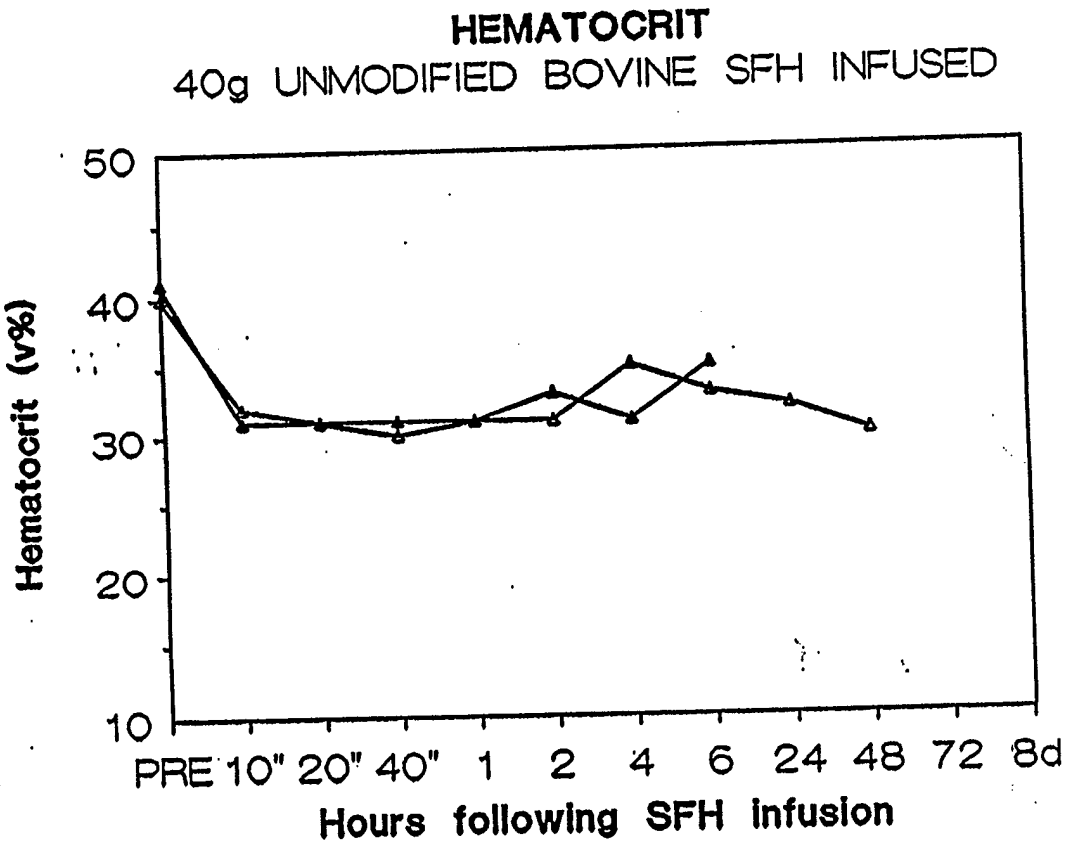
HEMATOCRIT
40g UNMODIFIED BOVINE SFH INFUSED
Hematocrit (v%)
50
40
30
20
10
PRE 10" 20" 40" 1 2 4 6 24 48 72 8d
Hours following SFH infusion

FIGURE 8

FIGURE 9

Peripheral venous hematocrit following infusion of modified bovine stroma-free hemoglobin.

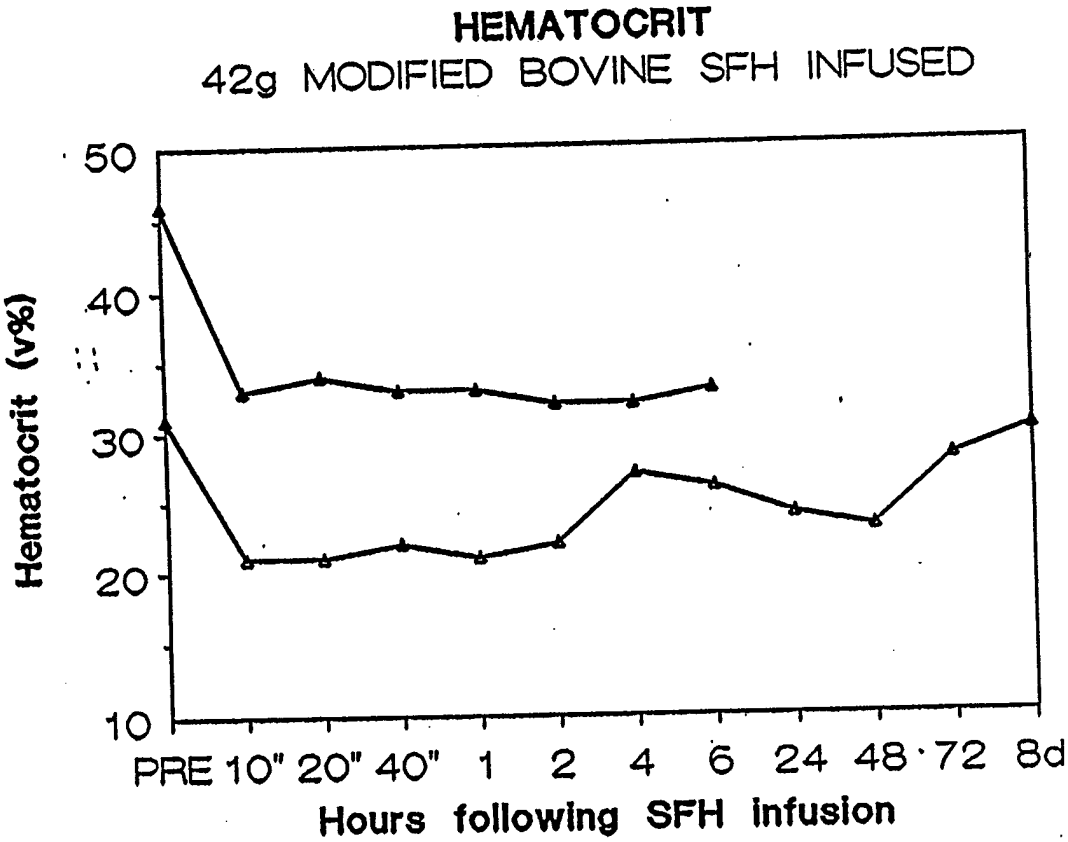
HEMATOCRIT
42g MODIFIED BOVINE SFH INFUSED
Hematocrit (v%)
50
40
30
20
10
PRE 10" 20" 40" 1 2 4 6 24 48 72 8d
Hours following SFH infusion

FIGURE 9

FIGURE 10

Plasma BUN following infusion of human DBBF stroma-free hemoglobin.

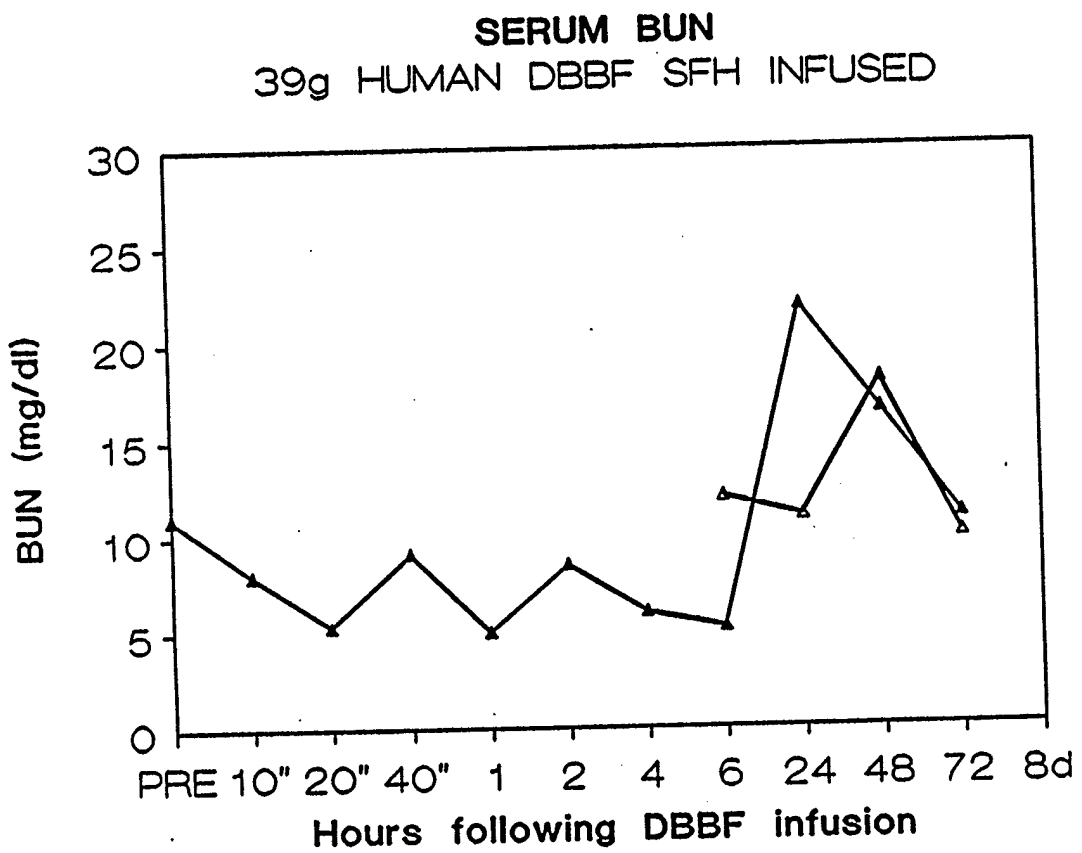
SERUM BUN
39g HUMAN DBBF SFH INFUSED
BUN (mg/dl)
30
25
20
15
10
5
0
PRE 10" 20" 40" 1 2 4 6 24 48 72 8d
Hours following DBBF infusion

FIGURE 10

FIGURE 11

Plasma BUN following infusion of unmodified bovine stroma-free hemoglobin.

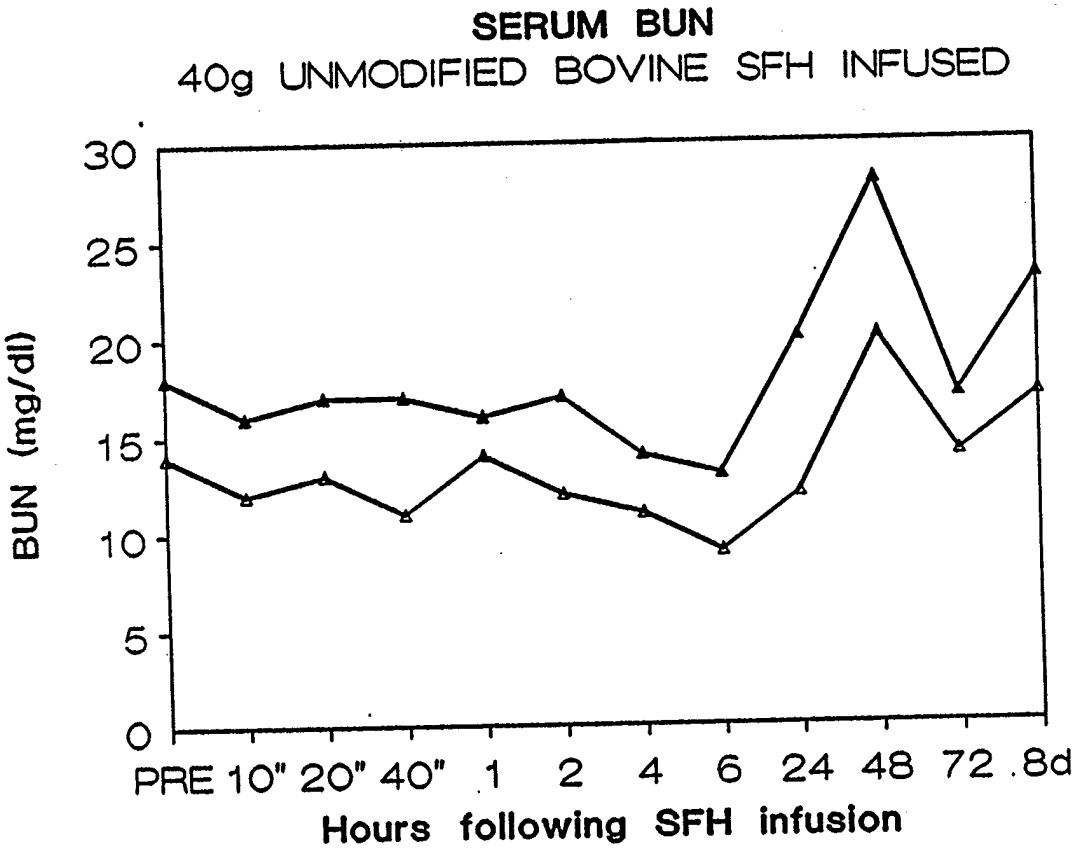
SERUM BUN
40g UNMODIFIED BOVINE SFH INFUSED
BUN (mg/dl)
30
25
20
15
10
5
0
PRE 10" 20" 40" 1 2 4 6 24 48 72 8d
Hours following SFH infusion

FIGURE 11

FIGURE 12

Plasma BUN following infusion of modified bovine stroma-free hemoglobin.

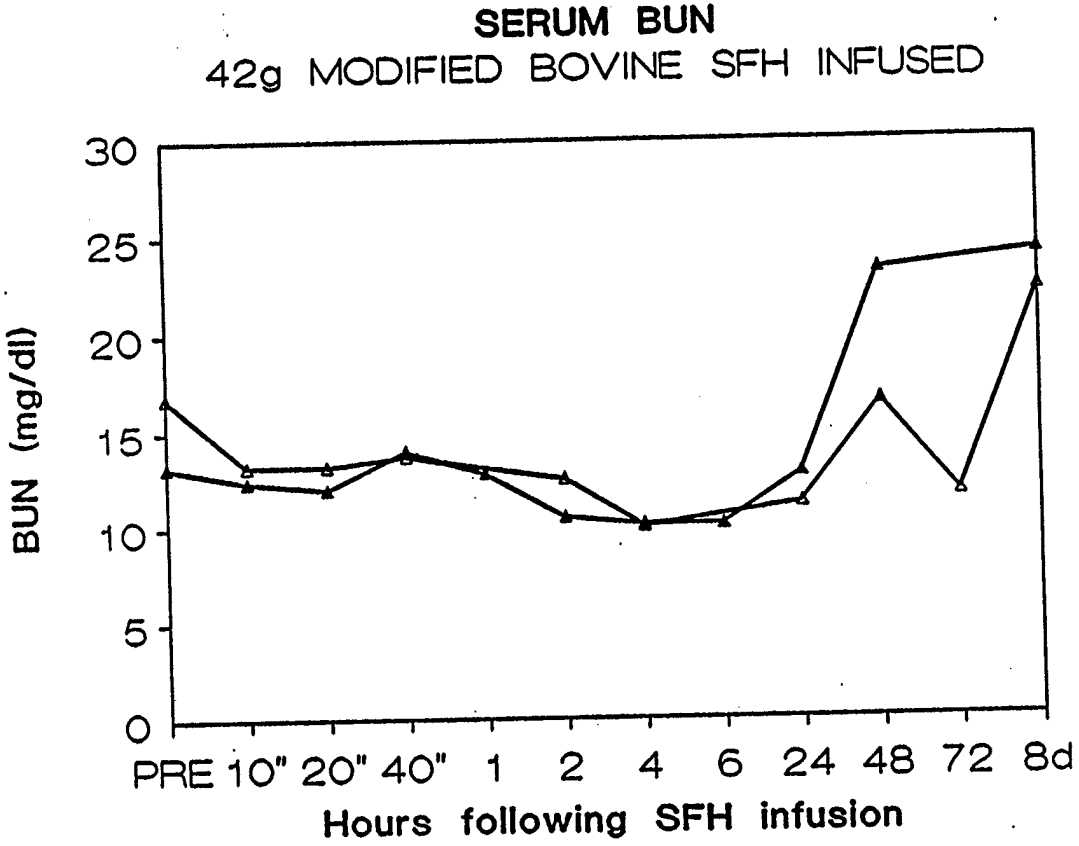
SERUM BUN
42g MODIFIED BOVINE SFH INFUSED
BUN (mg/dl)
30
25
20
15
10
5
0
PRE 10" 20" 40" 1 2 4 6 24 48 72 8d
Hours following SFH infusion

FIGURE 12

FIGURE 13

Plasma creatinine following infusion of human DBBF stroma-free hemoglobin.

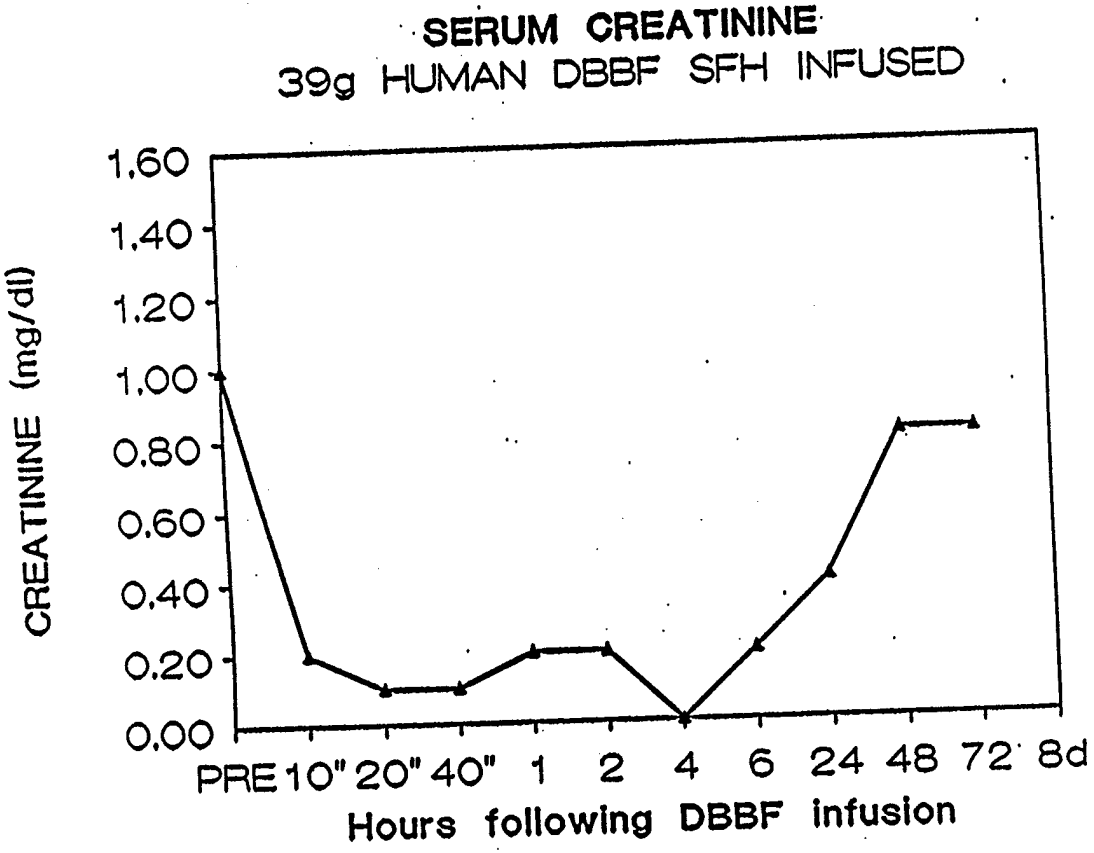
SERUM CREATININE
39g HUMAN DBBF SFH INFUSED
CREATININE (mg/dl)
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
PRE 10" 20" 40" 1 2 4 6 24 48 72 8d
Hours following DBBF infusion

FIGURE 13

FIGURE 14

Plasma creatinine following infusion of unmodified bovine stroma-free hemoglobin.

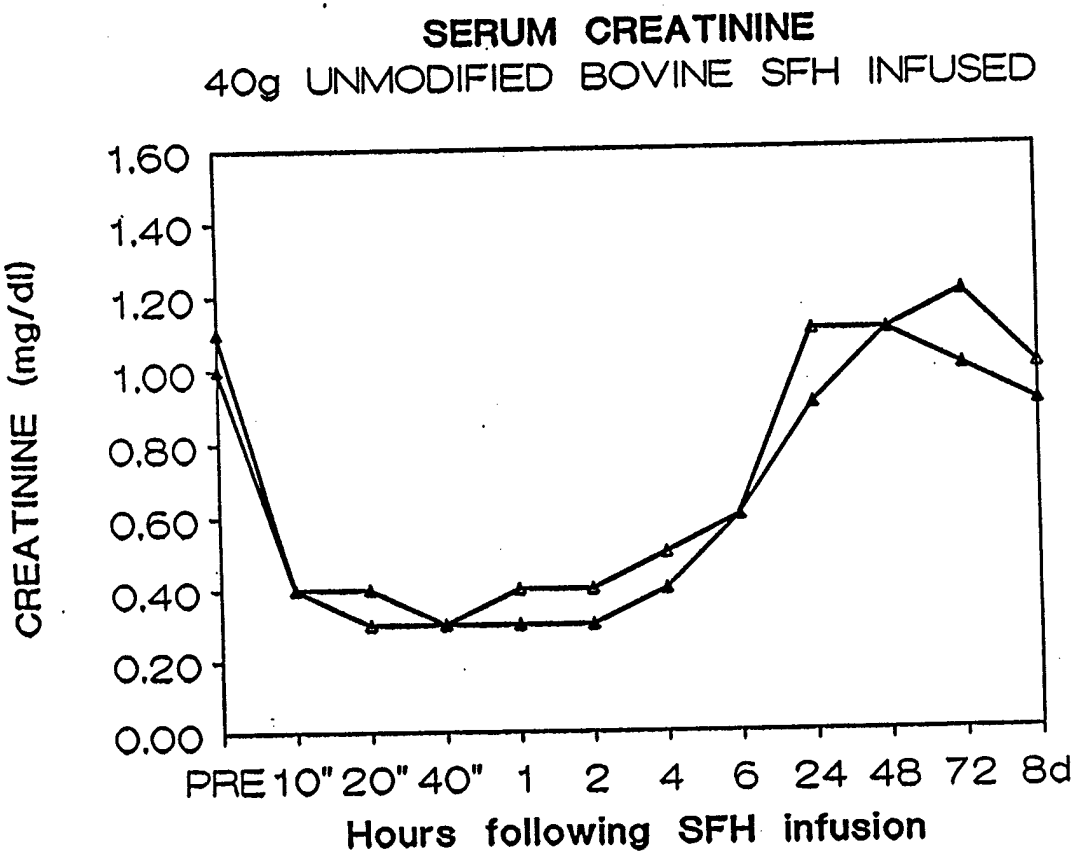
SERUM CREATININE
40g UNMODIFIED BOVINE SFH INFUSED
CREATININE (mg/dl)
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
PRE 10" 20" 40" 1 2 4 6 24 48 72 8d
Hours following SFH infusion

FIGURE 14

FIGURE 15

Plasma creatinine following infusion of modified bovine stroma-free hemoglobin.

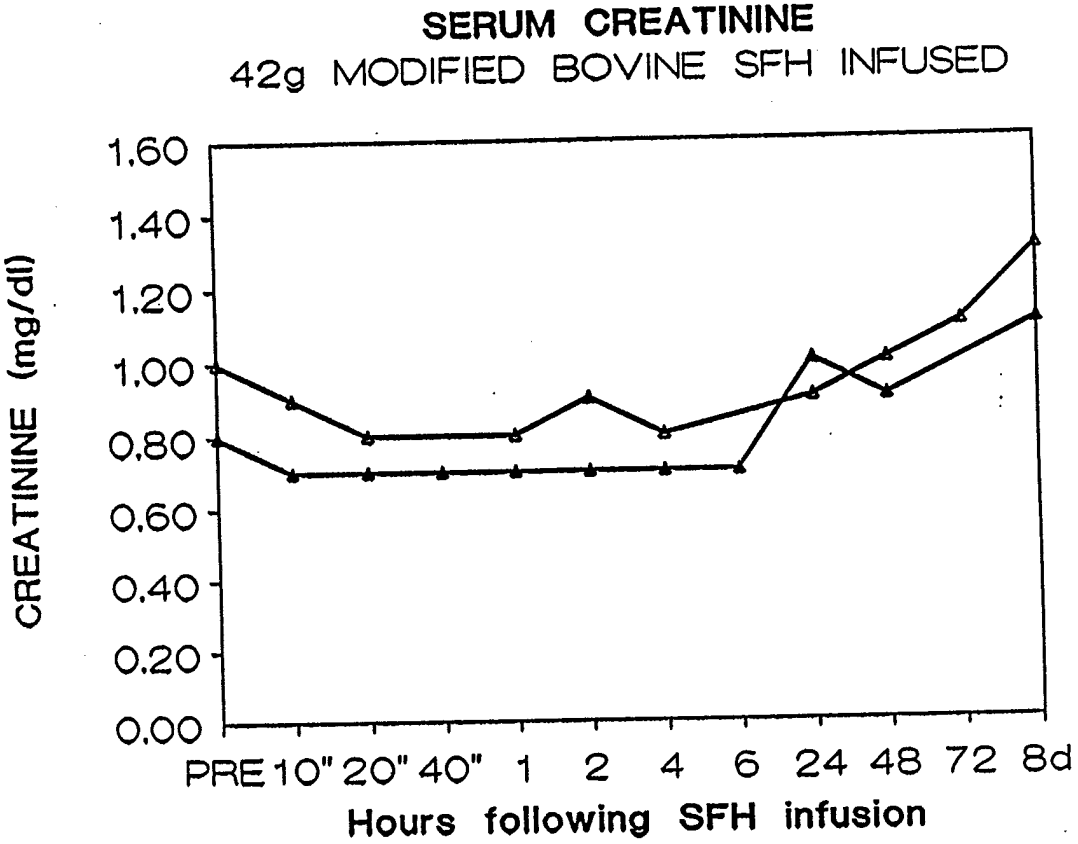
SERUM CREATININE
42g MODIFIED BOVINE SFH INFUSED
CREATININE (mg/dl)
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
PRE 10" 20" 40" 1 2 4 6 24 48 72 8d
Hours following SFH infusion

FIGURE 15

TABLE 1a

INFUSION OF 39G HUMAN STROMA-FREE HEMOGLOBIN (DBBF) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION										
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR	24 HR	48 HR	72 HR
Plasma hgb (mg/dl)	1.	35	35	2747	2324	2512	2567	2068	2197	2317	1748	502	219
	2.	20	15	----	1736	1435	1267	1633	1367	----	----	---	---
	Mean:	28	25	2747	2030	1917	1867	1851	1782	2317	1748	502	219
SFH recovery (%)	1.	--	--	90.9	64.1	63.3	61.0	54.0	59.0	56.4	37.9	10.3	5.0
	2.	--	--	----	61.0	48.5	41.5	45.0	39.2	----	----	----	---
	Mean:	--	--	90.9	62.6	55.9	51.3	49.5	49.1	56.4	37.9	10.3	5.0
Plasma MetHb (%)*	1.	--	--	30	33	31	28	26	19	19	--	--	--
	2.	--	--	--	26	30	26	19	15	--	--	--	--
	Mean:	--	--	30	30	31	27	23	17	19	--	--	--

*25% Methb infused

Table 1b

INFUSION OF 39G HUMAN STROMA-FREE HEMOGLOBIN (DBBF) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION										
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR	24 HR	48 HR	72 HR
Hgb (%)	1.	16.0	14.3	13.8	13.3	14.3	14.0	13.2	12.2	13.1	13.5	13.5	11.8
	2.	17.6	14.8	12.5	12.2	12.4	11.9	12.0	12.1	12.3	14.5	12.5	12.1
	Mean:	16.8	14.5	13.2	12:8	13.4	13.0	12.6	12.2	12.7	14.0	13.0	12.0
Hct (%)	1.	42.0	37.3	28.3	31.5	32.5	32.8	30.0	28.0	28.5	31.5	33.0	31.8
	2.	47.0	37.0	29.0	29.0	29.0	28.7	29.5	29.7	29.2	38.2	33.5	32.5
	Mean:	45.0	37.1	28.7	30.5	30.8	30.8	29.8	28.9	28.9	34.9	33.3	32.2
Serum BUN (mg/dl)	1.	11.0	11.0	8.0	5.3	9.1	5.0	8.5	6.0	5.2	21.8	16.5	11.0
	2.	----	----	---	---	---	---	---	---	12.1	10.8	18.4	10.0
	Mean:	11.0	11.0	8.0	5.3	9.1	5.0	8.5	6.0	8.7	16.3	17.5	10.5
Serum creatinine (mg/dl)	1.	1.1	0.90	0.2	0.1	0.1	0.2	0.2	0.0	0.2	0.4	0.8	0.8
	2.	.5	10.5	--	--	--	--	--	--	--	--	--	--
	Mean:	1.1	0.90	0.2	0.1	0.1	0.2	0.2	0.0	0.4	0.4	0.8	0.8

Table 1c

INFUSION OF 39G HUMAN STROMA-FREE HEMOGLOBIN (DBBF) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION											
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR	24 HR	48 HR	72 HR
Fibrinogen (mg/dl)	1.	127	120	49	79	80	82	80	240	85	230	550	440
	2.	125	110	70	71	74	68	71	74	80	---	540	530
Mean:		126	115	60	75	77	74	76	157	83	230	545	485
Factor 8 (%)	1.	424	298	242	226	200	214	190	192	186	632	632	544
	2.	500	304	191	174	162	171	181	167	154	---	412	472
Mean:		462	301	217	200	181	193	186	180	170	632	522	508
Platelet ($10^3/mm^3$)	1.	238	235	198	187	157	158	142	117	115	123	145	129
	2.	142	132	113	120	118	149	139	179	154	221	200	328
Mean:		190	184	156	154	138	154	141	148	135	172	173	229
WBC ($10^3/mm^3$)	1.	7.3	7.2	8.3	7.4	9.0	9.6	8.6	7.5	10.3	17.1	12.9	11.3
	2.	8.4	5.3	4.5	5.9	5.9	6.5	6.9	7.1	7.0	28.7	16.9	11.7
Mean:		7.9	6.3	6.4	6.7	7.5	8.1	7.8	7.3	8.7	22.9	14.9	11.5

Table 1d

INFUSION OF 39G HUMAN STROMA-FREE HEMOGLOBIN (DBBF) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION							
		BASE-LINE	10 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR	24 HR
Urine Hb (mg%)	1.	33	8	--	8	0	--	0	0
	2.	41	--	--	--	8	16	0	33
Urine Volume (ml)	1.	--	450	480	200	--	275	450	--
	2.	20	--	40	--	32	450	80	150
Urine Total Hb (mg)	1.	--	36	38	0	--	0	0	--
	2.	--	--	--	--	3	72	0	50
Urine BUN (mg/dl)	1.	1371	23	60	59	--	214	331	--
	2.	--	--	--	--	1159	452	245	--
Urine Creatinine (mg/dl)	1.	202	41	7	6	--	26	52	--
	2.	--	--	--	--	116	52	25	--
Creatinine Clearance (ml/min)	1.								
	2.					165 (avg of 6 hrs)			
BUN Clearance (ml/min)	1.	--	1294	79	107	--	177	248	--
	2.	--	--	--	--	--	60	--	--

Table 1e

INFUSION OF 39G HUMAN STROMA-FREE HEMOGLOBIN (DBBF) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION								
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR
MAP	1.	146	154	178	175	179	176	162	152	154
(mmHg)	2.	110	125	155	158	164	166	176	166	159
Mean:		128	140	167	167	172	171	169	159	156
apO2	1.	99	103	105	105	104	110	110	110	110
(mmHg)	2.	103	92	---	91	96	113	111	103	90
Mean:		101	98	105	98	100	112	111	107	100
apCO2	1.	34	33	28	28	27	26	25	24	24
(mmHg)	2.	37	36	36	40	39	37	30	24	26
Mean:		36	35	32	34	33	32	28	24	25
CVP	1.	1	1	1	2	1	0	1	0	1
(mmHg)	2.	7	15	12	12	10	8	9	9	5
Mean:		4	8	7	7	6	4	5	5	3
MPAP	1.	4	4	3	4	4	2	1	1	1
(mmHg)	2.	17	22	25	11	20	20	20	25	16
Mean:		11	14	14	7	11	11	11	13	9

Table 1f

INFUSION OF 39G HUMAN STROMA-FREE HEMOGLOBIN (DBBF) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION								
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR
A-V Difference (ml/dl)	1.	3.2	2.0	2.7	3.1	4.3	5.1	6.2	5.9	5.7
	2.	3.0	2.7	2.2	2.5	3.0	3.4	4.6	5.7	5.8
Mean:		3.1	2.4	2.5	2.8	3.7	4.3	5.4	5.8	5.8
O2 extra-tion (%)	1.	15.2	14.3	15.4	17.1	22.4	25.8	33.3	33.6	29.9
	2.	12.2	12.7	12.7	14.4	17.2	19.9	27.1	33.2	33.2
Mean:		13.7	13.5	14.1	15.8	19.8	22.9	30.2	33.4	31.6
CI L/min/kg	1.	0.15	0.15	0.13	0.14	0.11	0.08	0.08	0.08	0.09
	2.	0.29	0.26	0.27	0.25	0.19	0.16	0.12	0.10	0.09
Mean:		0.22	0.21	0.20	0.20	0.15	0.12	0.10	0.09	0.09
TPR (units)	1.	2.6	1.8	3.6	3.5	4.5	6.4	5.9	5.2	4.8
	2.	1.1	1.3	1.6	1.8	2.5	3.1	4.2	4.8	5.5
Mean:		1.9	1.6	2.6	2.7	3.5	4.7	5.1	5.0	5.2
HR beats/min	1.	243	198	141	137	104	87	78	70	72
	2.	249	238	188	187	169	151	224	154	148
Mean:		246	219	165	162	137	119	150	112	110

Table 1g

INFUSION OF 39G HUMAN STROMA-FREE HEMOGLOBIN (DBBF) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION								
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR
O2 Cons (ml/min/kg)	1.	3.9	3.3	3.1	3.5	3.8	3.2	3.8	3.8	4.1
	2.	7.3	5.7	4.9	5.2	4.9	4.4	4.7	4.8	4.2
Mean:		5.6	4.5	4.0	4.4	4.4	3.8	4.3	4.3	4.1
CO2 Prod (ml/min/kg)	1.	3.5	2.9	3.2	-0.7	2.6	2.6	2.2	2.6	2.8
	2.	4.6	3.0	-0.3	0.0	3.3	3.4	3.4	2.7	2.2
Mean:		4.1	3.0	1.5	-0.4	3.0	3.0	2.8	2.7	2.5
Deadspace (%)	1.	41	43	28	112	44	41	46	38	35
	2.	45	53	101	---	41	42	54	57	61
Mean:		43	48	65	112	43	42	50	48	48
Shunt (%)	1.	21	21	36	33	26	22	16	16	17
	2.	22	25	45	35	30	23	16	13	14
Mean:		22	23	41	34	28	23	16	15	16

Table 2a

INFUSION OF 40G OF NON-MODIFIED BOVINE STROMA-FREE HEMOGLOBIN (OXYPURE) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION												
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR	24 HR	48 HR	72 HR	8 DAY
Plasma Hb (mg/dl)	1.	13	102	1618	2044	2075	2033	1248	981	803	136	56	7	--
	2.	17	--	--	897	1616	1169	1438	968	716	312	79	17	5
Mean:		15			1470	1850	1597	1343	975	760	224	68	12	5
SFH recovery (%)	1.	--	--	49	62	63	62	38	30	24	4	2	--	--
	2.	--	--	--	30	54	39	48	32	24	10	3	--	--
Mean:		--	--	49	46	59	41	43	31	24	7	3	--	--
MetHb (%)	1.	1.5	1.7	1.9	1.8	1.6	1.7	1.6	1.4	1.5	--	--	--	--
	2.	2.5	2.5	2.9	2.9	2.7	2.7	2.6	2.3	2.3	--	--	--	--
Mean:		2.0	2.1	2.4	2.4	2.2	2.2	2.1	1.9	1.9				

Table 2b

INFUSION OF 40G OF NON-MODIFIED BOVINE STROMA-FREE HEMOGLOBIN (OXYPURE) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION												
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR	24 HR	48 HR	72 HR	8 DAY
Hb (g%)	1.	14.0	13.7	12.2	12.4	12.3	12.0	12.5	12.4	12.7				
	2.	14.6	--	13.0	13.0	13.0	12.0	12.0	13.0	12.0	12.0	11.0	--	--
Mean:		14.3	13.7	12.6	12.7	12.7	12.0	12.3	12.7	12.4	12.0	11.0	--	--
Hct (%)	1.	41	38	31	31	31	31	33	31	35	--	--	--	--
	2.	40	--	32	31	30	31	31	35	33	32	30	--	--
Mean:		41	38	32	31	31	31	32	33	34	32	30	--	--
Serum BUN (mg/dl)	1.	19	18	16	17	17	16	17	14	13	20	28	17	23
	2.	14	--	12	13	11	14	12	11	9	12	20	14	17
Mean:		17	18	14	15	14	15	15	13	11	16	24	16	20
Serum Creatinine (mg/dl)	1.	1.1	0.9	0.4	0.4	0.3	0.3	0.3	0.4	0.6	0.9	1.1	1.0	0.9
	2.	1.1	--	0.4	0.3	0.3	0.4	0.4	0.5	0.6	1.1	1.1	1.2	1.0
Mean:		1.1	0.9	0.4	0.4	0.3	0.4	0.4	0.5	0.6	1.0	1.1	1.1	1.0

Table 2c

INFUSION OF 40G OF UNMODIFIED BOVINE STROMA-FREE HEMOGLOBIN INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION										
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR	24 HR	48 HR	72 HR
Fibrinogen (mg/dl)	1.	130	100	70	74	75	76	85	83	110	430	450	300
	2.	--	--	--	--	--	--	--	--	--	--	--	--
Factor VIII (%)	1.	568	484	256	274	242	256	218	249	287	672	896	588
	2.	--	--	--	--	--	--	--	--	--	--	--	--
FDP (ug/ml)	1.	--	--	--	--	--	--	--	--	--	--	--	--
	2.	26	--	6	6	26	6	26	13	26	103	102	102
Platelet ($10^3/mm^3$)	1.	229	--	88	89	83	83	207	329	210	196	199	--
	2.	191	151	54	64	103	110	139	136	121	--	--	--
Mean:		210	151	71	77	93	97	173	233	166	196	199	--
WBC ($10^3/mm^3$)	1.	11.3	--	13.1	13.6	14.5	14.2	12.5	12.0	11.7	21.4	23.5	--
	2.	4.5	5.3	9.0	8.4	9.1	9.1	9.5	10.9	14.0	--	--	--
Mean:		7.9	5.3	11.1	11.0	11.8	11.7	11.0	11.5	12.9	21.4	23.5	--

Table 2d

INFUSION OF 40G OF NON-MODIFIED BOVINE STROMA-FREE HEMOGLOBIN (OXYPURE) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION											
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR	24 HR	48 HR	72 HR	8 DAY
Urine Hb (mg%)	1.	--	0	--	--	--	335	446	567	223	2	0	0	
	2.	33	65	--	569	537	700	732	553	455	--	0	--	
Urine Vol (ml)	1.	--	--	--	--	--	55	360	220	600	--	--	--	
	2.	--	--	10	10	10	100	600	500	800	--	250	--	
Urine Total Hb (mg)	1.	--	--	--	--	--	184	1606	1247	1338	--	--	--	
	2.	--	--	--	57	54	700	4392	2765	3640	--	--	--	
Urine BUN (mg/dl)	1.	895	--	--	--	--	305	274	252	333	249	922	771	901
	2.	2798	2398	3572	1659	933	865	681	148	124	--	1612	--	--
Urine Creatinine (mg/dl)	1.	92	--	--	--	--	25	22	18	28	14	98	81	98
	2.	267	217	308	186	106	79	65	15	13	--	163	--	--
Creatinine Clearance (ml/min)	1.	--	--	--	--	--	11	98	33	130	--	--	--	--
	2.	--	--	--	--	--	693	1667	136	142	--	--	--	--
BUN Clearance (ml/min)	1.	--	--	--	--	--	44	403	74	216	--	--	--	--
	2.	--	--	--	--	--	210	588	55	96				

Table 2e

INFUSION OF 40G OF NON-MODIFIED BOVINE STROMA-FREE HEMOGLOBIN (OXYPURE) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION								
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR
MAP (mmHg)	1.	153	154	183	184	181	177	175	172	156
	2.	140	130	193	197	206	212	207	192	81
Mean:		157	142	188	190	193	195	191	182	119
apO2 (mmHg)	1.	100	102	97	108	97	100	97	95	93
	2.	95	95	93	93	90	97	98	86	100
Mean:		98	99	95	101	94	99	98	91	97
apCO2 (mmHg)	1.	37	36	34	33	33	34	34	34	36
	2.	43	40	41	40	41	41	39	37	30
Mean:		40	38	38	37	37	38	37	36	33
CVP (mmHg)		--	--	--	--	--	--	--	--	--
MPAP (mmHg)		--	--	--	--	--	--	--	--	--

Table 2f

INFUSION OF 40G OF NON-MODIFIED BOVINE STROMA-FREE HEMOGLOBIN (OXYPURE) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION								
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR
A-V	1.	3.6	3.0	4.1	4.5	4.8	5.9	6.4	6.8	8.9
	2.	2.8	2.5	2.6	2.9	3.5	3.9	4.3	--	6.2
Mean:		3.2	2.8	3.4	3.7	4.2	4.9	5.4	6.8	7.6
O2 Extra-	1.		16.0	24.2	26.9	29.3	34.9	37.4	41.1	50.9
ction	2.	14.6	13.6	15.0	17.0	24.0	23.2	25.1	--	16.4
Mean:		14.6	14.8	19.6	22.0	24.9	29.1	31.3	41.1	33.7
CI	1.	.11	.14	.12	.10	.09	.09	.07	.09	.10
L/min/kg	2.	.23	.31	.27	.24	.21	.16	.13	.10	.09
Mean:		.17	.22	.20	.17	.15	.13	.10	.10	.10
TPR	1.	4.0	3.1	4.2	5.3	5.9	5.4	6.8	5.5	4.7
units	2.	1.7	1.2	2.0	2.2	2.7	3.7	4.3	5.4	2.3
Mean:		2.9	2.2	3.1	3.7	4.3	4.6	5.6	5.5	3.5
HR	1.	123	116	107	100	88	97	96	149	167
beats/min	2.	185	192	255	201	151	123	112	107	91
Mean:		154	154	181	150	120	110	104	128	129

Table 2g

INFUSION OF 40G OF NON-MODIFIED BOVINE STROMA-FREE HEMOGLOBIN (OXYPURE) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION								
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR
O2 Cons ml/min/kg	1.	3.4	3.6	4.3	0.2	3.6	4.6	3.9	5.0	7.1
	2.	5.4	6.4	5.8	5.8	6.0	5.0	4.7	---	4.8
Mean:		4.4	5.0	5.1	3.0	4.8	4.8	4.3	5.0	6.0
CO2 Production ml/min/kg	1.	1.9	0.3	2.1	0.1	2.5	1.8	2.1	4.1	6.2
	2.	5.0	4.7	4.4	0	3.9	3.6	3.6	3.5	4.2
Mean:		3.5	2.5	3.3	0.1	3.2	5.4	2.9	3.8	5.2
Deadspace		49.1	46.5	44.4	2.7	52.1	49.2	45.5	45	42
Shunt (%)	1.	18.4	-2.7	13.4	14.4	12.5	11.5	9.1	10.7	11.5
	2.	52.6	52.1	48.1	46.1	50.0	41.9	36.6	--	23
Mean:		35.5	24.7	30.8	30.3	31.3	26.7	22.9	10.7	17.3

Table 3a

INFUSION OF 42G MODIFIED BOVINE STROMA-FREE HEMOGLOBIN (HEMOPURE) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION											
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR	24 HR	48 HR	72 HR	8DAY
Plasma Hb (mg/dl)	1.	14	11	2049	1914	1947	1960	1732	1579	237	298	330	---	28
	2.	--	--	860	885	859	910	865	863	862	610	322	84	--
Mean:		14	11	1450	1400	2806	1435	1299	1221	550	298	330	84	28
SFH Recovery (%)	1.	--	--	63	59	58	56	50	47	5	9	9	---	--
	2.	--	--	23	24	23	29	27	27	27	19	10	3	--
Mean:		--	--	43	42	41	44	39	37	16	14	10	3	--
Met Hb (%)	1.	1.6	1.5	2.4	2.4	1.9	2.1	2.0	1.8	1.9	---	---	---	
	2.	1.6	1.6	3.5	3.3	3.7	3.7	3.7	3.6	3.2	3.2	---	---	
Mean:		1.6	1.6	3.1	2.9	2.8	2.9	2.8	2.5	2.6	---	---	---	

Table 3b

INFUSION OF 42G MODIFIED BOVINE STROMA-FREE HEMOGLOBIN (HEMOPURE) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION												
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR	24 HR	48 HR	72 HR	8DAY
Hb (g%)	1.	16.7	15.1	13.1	13.4	12.9	13.3	13.1	13.1	12.7		---	---	--
	2.	11.8	---	9.6	10.0	9.9	9.6	9.9	11.3	10.6	9.6	8.9	10.9	12.0
Mean:		12.8	15.1	11.4	11.7	11.4	11.5	11.4	12.2	11.7	9.6	8.9	10.9	12.0
Hct (%)	1.	46	43	33	34	33	33	32	32	33	---	---	---	---
	2.	31	--	21	21	22	21	22	27	26	24	23	28	30
Mean:		39	43	27	28	28	27	27	30	30	24	23	28	30
Serum BUN (mg/dl)	1.	15.4	13.2	12.4	12.0	14.0	12.8	10.5	10.1	10.1	12.8	23.2	--	24.1
	2.	16.8	--	13.2	13.2	13.7	3.8	12.5	10.0	2.1	11.2	16.5	11.7	22.2
Mean:		16.1	13.2	12.8	12.6	13.9	8.3	11.5	10.1	6.1	12.0	20.0	11.7	23.2
Serum Creat-inine (mg/dl)	1.	0.9	0.8	0.7	0.7	0.7	0.7	0.7	0.7	0.7	1.0	0.9	--	1.1
	2.	1.0	--	0.9	0.8	10.0	0.8	0.9	0.8	0.1	0.9	1.0	1.1	1.3
Mean:		1.0	0.8	0.8	0.8	0.9	0.8	0.8	0.8	0.5	1.0	1.0	1.1	1.2

Table 3c

INFUSION OF 42G MODIFIED BOVINE STROMA-FREE HEMOGLOBIN (HEMOPURE) INTO DOGS WITH SPLEENS

		BASE-LINE	PRE-INFUSION	TIME AFTER SFH INFUSION 10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR	24 HR	48 HR	72 HR
Fibrinogen	1.	120	120	62	71	70	70	69	72	85	340	410	210
(mg/dl)	2.	215	--	120	120	115	110	105	130	140	300	360	600
Mean:		168		91	96	93	90	87	101	113	320	385	405
Factor VIII	1.	304	408	238	242	264	244	196	184	162	500	478	624
(%)	2.	796	--	170	178	182	212	178	212	262	376	472	688
Mean:		550		204	210	223	228	187	198	212	438	475	656
FDP	1.	13	8	13	3	3	-1	2	13	--	51	102	26
(ug/ml)	2.	205	--	102	51	102	102	--	102	102	205	410	--
Platelet ($10^3/mm^3$)	1.	180	158	72	85	92	139	155	153	159	--	--	--
	2.	293	--	91	153	153	133	195	196	218	153	153	236
Mean:		237	158	82	119	123	136	175	175	189	153	153	236
WBC ($10^3/mm^3$)	1.	4.9	5.4	5.3	5.7	6.0	6.8	6.7	6.9	8.0	--	--	--
	2.	6.4	--	3.8	4.5	5.0	5.3	5.8	6.1	7.1	10.2	8.5	10.5
Mean:		5.7	5.4	4.6	5.1	5.5	6.1	6.3	6.5	7.6	10.2	8.5	10.5

Table 3d

INFUSION OF 42G MODIFIED BOVINE STROMA-FREE HEMOGLOBIN (HEMOPURE) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION											
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR	24 HR	48 HR	72 HR	8 DAY
Urine Hb (mg%)	1.	--	--	676	708	830	708	1204	--	732	2440	--	--	8
	2.	41	--	--	--	--	766	--	407	350	8	16	16	--
Urine Vol (ml)	1.	--	--	17	14	17	15	150	--	150	240	--	--	--
	2.	--	--	--	--	--	75	--	800	130	350	100	150	--
Urine Total Hb (mg)	1.	--	--	115	99	141	106	1860	--	1098	--	--	--	--
	2.	--	--	--	--	--	575	--	3526	455	28	16	--	--
Urine BUN (mg/dl)	1.	--	--	2339	1865	1331	1478	1637	--	1228	533	--	--	628
	2.	--	1715	1218	--	--	--	--	279	279	380	1066	1072	--
Urine Creatinine (mg/dl)	1.	--	--	168	116	106	103	122	--	110	37	--	--	46
	2.	--	184	110	--	--	--	--	21	24	43	82	105	--
Creatinine Clearance (ml/min)	1.	--	--	130	--	--	113	442	--	103	--	--	--	--
	2.	--	--	--	--	--	--	--	117	527	--	--	--	--
BUN Clearance (ml/min)	1.	--	--	106	--	--	92	390	--	77	--	--	--	--
	2.	--	--	--	--	--	--	--	124	144	--	--	--	--

Table 3e

INFUSION OF 42G MODIFIED BOVINE STROMA-FREE HEMOGLOBIN (HEMOPURE) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION								
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR
MAP	1.	120	127	163	159	155	154	156	158	150
(mmHg)	2.	147	148	154	164	174	71	168	158	156
Mean:		133	138	159	162	165	113	162	158	153
apO2	1.	89	83	97	101	92	93	90	93	91
(mmHg)	2.	98	102	95	95	94	93	91	92	87
Mean:		95	93	96	98	93	93	91	92	89
apCO2	1.	41	41	40	40	38	39	40	35	35
(mmHg)	2.	30	28	29	31	28	29	30	28	28
Mean:		36	35	34	36	33	34	35	32	32
CVP	1.	5	5	5	6	5	6	4	5	5
(mmHg)	2.	10	8	12	13	13	12	11	2	5
Mean:		8	7	8	9	9	9	8	4	5
MPAP	1.	17	10	16	12	10	8	6	8	7
(mmHg)	2.	18	22	21	21	21	20	15	6	12
Mean:		18	16	19	17	16	14	11	7	10

Table 3f

INFUSION OF 42G MODIFIED BOVINE STROMA-FREE HEMOGLOBIN (HEMOPURE) INTO DOGS WITH SPLEENS

		TIME AFTER SFH INFUSION								
		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR
A-V Difference (ml/dl)	1.	3.8	3.6	2.0	2.1	2.6	3.3	3.9	5.0	5.1
	2.	1.1	0.7	4.2	4.0	2.1	2.6	2.1	5.2	5.5
Mean:		2.5	2.2	3.1	3.1	2.4	3.0	3.0	5.1	5.3
O2 Extraction(%)	1.	16.0	16.8	10.9	11.5	14.6	18.4	21.6	28.3	29.9
	2.	22.6	18.1	33.0	29.2	31.6	31.9	29.1	38.2	38.8
Mean:		19.3	17.5	22.0	20.4	23.1	25.2	25.4	33.2	34.4
CI L/min/kg	1.	.26	.26	.32	.25	.19	.14	.12	.10	.10
	2.	.11	.17	.13	.10	.11	.11	.07	.05	.08
Mean:		.19	.22	.23	.18	.15	.13	.10	.08	.09
TPR units	1.	2.0	1.1	1.2	1.4	1.9	2.6	3.1	3.5	3.3
	2.	3.0	2.1	2.7	3.7	3.7	1.4	5.6	8.3	4.6
Mean:		2.0	1.6	2.0	2.6	2.8	2.0	4.4	5.9	4.0
HR beats/min	1.	215	236	171	157	110	110	73	63	62
	2.	160	161	152	117	115	126	167	173	177
Mean:		188	199	162	137	113	118	120	118	120

Table 3g

INFUSION OF 42G MODIFIED BOVINE STROMA-FREE HEMOGLOBIN (HEMOPURE) INTO DOGS WITH SPLEENS

		BASE-LINE	PRE-INFUSION	10 MIN	20 MIN	40 MIN	1 HR	2 HR	4 HR	6 HR
O2 Cons	1.	8.4	7.7	5.2	4.4	4.0	3.8	3.8	4.3	4.5
ml/min/kg	2.	3.2	3.2	4.6	2.9	3.7	3.8	2.2	1.9	3.6
Mean:		5.8	5.5	5.9	3.7	3.9	3.8	3.0	3.1	4.1
CO2 Prod	1.	9.4	7.0	7.8	0	4.8	1.7	2.1	2.5	2.8
ml/min/kg	2.	--	--	--	-	--	--	--	--	--
Mean:										
Deadspace	1.	108.1	--	31.3	2.8	36.9	2.9	56.4	53.1	53.1
(%)	2.	110.4	112.0	3.9	3.7	65.0	54.9	54.7	57.5	52.8
Mean:		109.0	112.0	17.1	3.3	50.9	29.0	55.6	55.3	53.0
Shunt	1.	24.2	28.3	35.8	26.6	25.6	21.8	22.2	15.1	14.4
(%)	2.	12.1	14.8	17.5	17.2	17.6	18.0	19.6	14.9	15.2
Mean:		18.2	21.6	26.7	21.9	21.6	19.9	20.9	15.0	14.8

Table 4

INCREASE IN BUN LEVEL AND THE PLASMA HEMOGLOBIN CONCENTRATION 24 TO 48 HOURS FOLLOWING SFH INFUSION

Hemoglobin concentration Infused	Serum BUN mg/dl Pre	48 hr	% Increase 48 hr	Plasma Hemoglobin (mg/dl) 24 hr	48 hr
DBBF	11	17	50	1742	502
Mod BSFH	16	20	25	298	330
Unmod BSFH	17	24	29	224	68

Table 5

IN VITRO EFFECT OF THE PRESENCE OF HEMOGLOBIN ON THE MEASUREMENT OF BUN IN DOG SERUM

BUN measurments in 5 aliquots of a serum samples containing increasing hemoglobin concentrations in a constant volume of 1.2 ml

Aliquot	Hemoglobin (mg/dl)	Serum BUN (mg/dl)	Serum BUN (% increase above aliquot 1)
Experiment 1.			
1	0	12.5	--
2	207	12.6	0.8
3	517	13.6	8.8
4	1034	13.8	10.4
5	2067	13.2	5.6
Experiment 2.			
1	0	6.5	--
2	210	6.7	3.7
3	525	6.7	4.0
4	1050	7.9	21.7
5	2100	9.1	41.7